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FILE 'BIOSIS' ENTERED AT 16:21:46 ON 19 SEP 2002
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FILE 'SCISEARCH' ENTERED AT 16:21:46 ON 19 SEP 2002
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FILE 'MEDLINE' ENTERED AT 16:21:46 ON 19 SEP 2002

FILE 'USPATFULL' ENTERED AT 16:21:46 ON 19 SEP 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=> s (tumor necrosis factor receptor 1) or tnfr1
L1        2194 (TUMOR NECROSIS FACTOR RECEPTOR 1) OR TNFR1

=> s antisense or (complement? (2n) oligonucl?)
L2      103357 ANTISENSE OR (COMPLEMENT? (2N) OLIGONUCL?)

=> s (tumor necrosis factor receptor 1) or tnfr1  or (tnf (2n) receptor (2n) 1)
   4 FILES SEARCHED...
L3        4155 (TUMOR NECROSIS FACTOR RECEPTOR 1) OR TNFR1 OR (TNF (2N) RECEPTO
               R (2N) 1)

=> s l2 and l3
L4         298 L2 AND L3

=> s l2 (s) l3
L5          38 L2 (S) L3

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6          21 DUP REM L5 (17 DUPLICATES REMOVED)

=> s l6 and py<=1998
   1 FILES SEARCHED...
   4 FILES SEARCHED...
L7           5 L6 AND PY<=1998

=> d l6 1-21 ibib abs

L6   ANSWER 1 OF 21  CA  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        137:57583  CA
TITLE:                   Antisense modulation of tumor necrosis factor
                         receptor-1 (TNFR1) expression for treatment of
                         diseases
INVENTOR(S):             Baker, Brenda F.; Cowsert, Lex M.; Zhang, Hong; Dean,
                         Nicholas M.
PATENT ASSIGNEE(S):      Isis Pharmaceuticals, Inc., USA
SOURCE:                  PCT Int. Appl., 121 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
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WO 2002048168 A1 20020620 WO 2001-US51224 20011022
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2000-695451 A 20001024

AB Antisense compds., compns. and methods are provided for modulating the expression of TNFR1. The compns. comprise antisense compds., particularly antisense oligonucleotides, targeted to nucleic acids encoding TNFR1. Methods of using these compds. for modulation of TNFR1 expression and for treatment of diseases assocd. with expression of TNFR1 are provided. Diseases treated were liver injury, hepatitis and liver cancer.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 21 USPATFULL

ACCESSION NUMBER: 2002:126317 USPATFULL
TITLE: Human tumor necrosis factor delta and epsilon
INVENTOR(S): Yu, Guo-Liang, Berkeley, CA, UNITED STATES
Ni, Jian, Germantown, MD, UNITED STATES
Gentz, Reiner L., Rockville, MD, UNITED STATES
Dillon, Patrick J., Carlsbad, CA, UNITED STATES
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002064829 | A1 | 20020530 |
| APPLICATION INFO.: | US 2001-879919 | A1 | 20010614 (9) |

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1997-815783, filed on 12 Mar 1997, PENDING

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1996-16812P | 19960314 (60) |
| | US 2001-293499P | 20010525 (60) |
| | US 2001-277978P | 20010323 (60) |
| | US 2001-276248P | 20010316 (60) |
| | US 2000-254875P | 20001213 (60) |
| | US 2000-241952P | 20001023 (60) |
| | US 2000-211537P | 20000615 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 62
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 13531
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to human TNF delta and TNF epsilon polypeptides, polynucleotides encoding the polypeptides, methods for producing the polypeptides, in particular by expressing the polynucleotides, and agonists and antagonists of the polypeptides. The invention further relates to methods for utilizing such polynucleotides, polypeptides, agonists and antagonists for applications, which relate, in part, to research, diagnostic and clinical arts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 3 OF 21 USPATFULL

ACCESSION NUMBER: 2002:119846 USPATFULL

TITLE: Human G-protein Chemokine receptor (CCR5) HDGNR10

INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Roschke, Viktor, Rockville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2002061834 | A1 | 20020523 | |
| APPLICATION INFO.: | US 2001-779880 | A1 | 20010209 | (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2000-181258P | 20000209 (60) |
| | US 2000-187999P | 20000309 (60) |
| | US 2000-234336P | 20000922 (60) |

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: STERNE, KESSLER, GOLDSTEIN & FOX PLLC, 1100 NEW YORK AVENUE, N.W., SUITE 600, WASHINGTON, DC, 20005-3934

NUMBER OF CLAIMS: 61

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 4 Drawing Page(s)

LINE COUNT: 18667

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel human protein called Human G-protein Chemokine Receptor (CCR5) HDGNR10, and isolated polynucleotides encoding this protein. The invention is also directed to human antibodies that bind Human G-protein Chemokine Receptor (CCR5) HDGNR10 and to polynucleotides encoding those antibodies. Also provided are vectors, host cells, antibodies, and recombinant methods for producing Human G-protein Chemokine Receptor (CCR5) HDGNR10 and human anti-Human G-protein Chemokine Receptor (CCR5) HDGNR10 antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to this novel human protein and these novel human antibodies.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 4 OF 21 USPATFULL

ACCESSION NUMBER: 2002:92268 USPATFULL

TITLE: Human G-protein Chemokine Receptor HDGNR10

INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Roschke, Viktor, Rockville, MD, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2002048786 | A1 | 20020425 | |
| APPLICATION INFO.: | US 2001-779879 | A1 | 20010209 | (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2000-181258P | 20000209 (60) |
| | US 2000-187999P | 20000309 (60) |
| | US 2000-234336P | 20000922 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STERNE, KESSLER, GOLDSTEIN & FOX PLLC, 1100 NEW YORK AVENUE, N.W., SUITE 600, WASHINGTON, DC, 20005-3934
NUMBER OF CLAIMS: 61
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 17969
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel human protein called Human G-protein Chemokine Receptor (CCR5) HDGNR10, and isolated polynucleotides encoding this protein. The invention is also directed to human antibodies that bind Human G-protein Chemokine Receptor (CCR5) HDGNR10 and to polynucleotides encoding those antibodies. Also provided are vectors, host cells, antibodies, and recombinant methods for producing Human G-protein Chemokine Receptor (CCR5) HDGNR10 and human anti-Human G-protein Chemokine Receptor (CCR5) HDGNR10 antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to this novel human protein and these novel human antibodies.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 5 OF 21 USPATFULL
ACCESSION NUMBER: 2002:27093 USPATFULL
TITLE: Methods for identifying inhibitors of neuronal degeneration
INVENTOR(S): McCarthy, Justin, Mountain View, CA, UNITED STATES
Cordell, Barbara, Palo Alto, CA, UNITED STATES

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002015939 | A1 | 20020207 |
| APPLICATION INFO.: | US 2001-754949 | A1 | 20010104 (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2000-175200P | 20000110 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KNOBBE MARTENS OLSON & BEAR LLP, 620 NEWPORT CENTER DRIVE, SIXTEENTH FLOOR, NEWPORT BEACH, CA, 92660
NUMBER OF CLAIMS: 52
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 33 Drawing Page(s)
LINE COUNT: 2165
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention concerns methods and means for identifying inhibitors of neuronal degeneration, and their use in the treatment of neurodegenerative disorders. In particular the invention concerns methods and means for identifying inhibitors of neuronal degeneration or cell death by taking advantage of the involvement of presenilin (PS) and Par-4 in NF-.kappa.B activation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 6 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:395944 BIOSIS
DOCUMENT NUMBER: PREV200200395944
TITLE: Functional dissection of both Fas and **TNFR1** apoptotic signaling pathways in mouse liver using **antisense** oligonucleotides.

AUTHOR(S): Zhang, Hong (1); Luther, Doreen (1); Conklin, Boyd (1); Lemonidis, Kristina (1); Bennett, C. Frank (1); Freier, Sue (1); Dean, Nicholas M. (1)
CORPORATE SOURCE: (1) Isis Pharmaceuticals, Carlsbad, CA USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 711. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L6 ANSWER 7 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2002:484522 BIOSIS
DOCUMENT NUMBER: PREV200200484522
TITLE: Identification of ARTS-1 as a novel TNFR1-binding protein that promotes TNFR1 ectodomain shedding.
AUTHOR(S): Cui, Xinle; Hawari, Feras; Alsaaty, Sura; Lawrence, Marion; Combs, Christian A.; Geng, Weidong; Rouhani, Farshid N.; Miskinis, Dianne; Levine, Stewart J. (1)
CORPORATE SOURCE: (1) Pulmonary-Critical Care Medicine Branch, NHLBI, National Institutes of Health, 10 Center Drive, Room 6D03, MSC 1590, Bethesda, MD, 20892-1590: levines@nih.gov USA
SOURCE: Journal of Clinical Investigation, (August, 2002) Vol. 110, No. 4, pp. 515-526. http://www.jci.org/. print.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Proteolytic cleavage of **TNF receptor 1** (**TNFR1**) generates soluble receptors that regulate TNF bioactivity. We hypothesized that the mechanism of **TNFR1** shedding might involve interactions with regulatory ectoproteins. Using a yeast two-hybrid approach, we identified ARTS-1 (aminopeptidase regulator of **TNFR1** shedding) as a type II integral membrane protein that binds to the **TNFR1** extracellular domain. In vivo binding of membrane-associated ARTS-1 to **TNFR1** was confirmed by coimmunoprecipitation experiments using human pulmonary epithelial and umbilical vein endothelial cells. A direct relationship exists between membrane-associated ARTS-1 protein levels and concordant changes in **TNFR1** shedding. Cells overexpressing ARTS-1 demonstrated increased **TNFR1** shedding and decreased membrane-associated **TNFR1**, while cells expressing **antisense** ARTS-1 mRNA demonstrated decreased membrane-associated ARTS-1, decreased **TNFR1** shedding, and increased membrane-associated **TNFR1**. ARTS-1 neither bound to TNFR2 nor altered its shedding, suggesting specificity for **TNFR1**. Although a recombinant ARTS-1 protein demonstrated selective aminopeptidase activity toward non-polar amino acids, multiple lines of negative evidence suggest that ARTS-1 does not possess **TNFR1** sheddase activity. These data indicate that ARTS-1 is a multifunctional ectoprotein capable of binding to and promoting **TNFR1** shedding. We propose that formation of a **TNFR1**-ARTS-1 molecular complex represents a novel mechanism by which **TNFR1** shedding is regulated.

L6 ANSWER 8 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2002:363691 BIOSIS
DOCUMENT NUMBER: PREV200200363691
TITLE: DAP kinase and DRP-1 mediate membrane blebbing and the formation of autophagic vesicles during programmed cell

death.
AUTHOR(S): Inbal, Boaz; Bialik, Shani; Sabanay, Ilana; Shani, Gidi; Kimchi, Adi (1)
CORPORATE SOURCE: (1) Dept. of Molecular Genetics, Weizmann Institute of Science, Rehovot, 76100: Adi.kimchi@weizmann.ac.il Israel
SOURCE: Journal of Cell Biology, (April 29, 2002) Vol. 157, No. 3, pp. 455-468. http://www.jcb.org/. print.
ISSN: 0021-9525.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Death-associated protein kinase (DAPk) and DAPk-related protein kinase (DRP)-1 proteins are Ca+2/calmodulin-regulated Ser/Thr death kinases whose precise roles in programmed cell death are still mostly unknown. In this study, we dissected the subcellular events in which these kinases are involved during cell death. Expression of each of these DAPk subfamily members in their activated forms triggered two major cytoplasmic events: membrane blebbing, characteristic of several types of cell death, and extensive autophagy, which is typical of autophagic (type II) programmed cell death. These two different cellular outcomes were totally independent of caspase activity. It was also found that dominant negative mutants of DAPk or DRP-1 reduced membrane blebbing during the p55/**tumor necrosis factor receptor 1**-induced type I apoptosis but did not prevent nuclear fragmentation. In addition, expression of the dominant negative mutant of DRP-1 or of DAPk **antisense** mRNA reduced autophagy induced by antiestrogens, amino acid starvation, or administration of interferon-gamma. Thus, both endogenous DAPk and DRP-1 possess rate-limiting functions in these two distinct cytoplasmic events. Finally, immunogold staining showed that DRP-1 is localized inside the autophagic vesicles, suggesting a direct involvement of this kinase in the process of autophagy.

L6 ANSWER 9 OF 21 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:238607 CA
TITLE: Cloning, characterization and therapeutic applications of ARTS-1, sheddase of TNF type I receptor and other cytokine receptors
INVENTOR(S): Levine, Stewart
PATENT ASSIGNEE(S): Government of the United States of America, as Represented by the Secretary, Department of Health and Human Services, USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001064856 | A2 | 20010907 | WO 2001-US6464 | 20010228 |
| WO 2001064856 | A3 | 20020418 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-185586P P 20000228
AB The present invention provides compns. and methods for the regulation of

cytokine signaling through the tumor necrosis factor (TNF) pathway. Specifically, the invention provides a novel gene, polypeptide and related compns. and methods for the regulation of ectodomain shedding. Specifically, the invention provides a novel polypeptide and a gene which encodes the polypeptide, which has the ability to promote the shedding of the extracellular domain of type I TNF receptor (TNFR1). This polypeptide and gene are called ARTS-1, for aminopeptidase regulator of type I, 55 kDa TNF receptor ectodomain shedding. Cloning, amino acid and encoding cDNA sequences of human ARTS-1 are disclosed. The open reading frame predicted from the human ARTS-1 cDNA encodes a protein of 941 amino acid residues. The patterns of tissue expression of the endogenous ARTS-1 and recombinant ARTS-1 expression in cultured cell lines are described. ARTS-1 TNFR1 ectodomain sheddase regulatory activity is analyzed. It is contemplated that ARTS-1 will also regulate the shedding of ectodomains of other cytokine receptors including IL-1RII and IL-6R. In preferred embodiments, methods and compns. for the regulation of TNFR1 ectodomain shedding are provided. The present invention finds use in therapeutics, diagnostics, and drug screening applications.

L6 ANSWER 10 OF 21 USPATFULL

| | |
|---|---|
| ACCESSION NUMBER: | 2001:237482 USPATFULL |
| TITLE: | Use of certain drugs for treating nerve root injury |
| INVENTOR(S): | Olmarker, Kjell, Molndal, Sweden<br>Rydevik, Bjorn, Goteborg, Sweden |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2001055594 | A1 | 20011227 |
| APPLICATION INFO.: | US 2001-826893 | A1 | 20010406 (9) |

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-743852, filed on 17 Jan 2001, PENDING A 371 of International Ser. No. WO 1999-SE1671, filed on 23 Sep 1999, UNKNOWN

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | SE 1998-3276 | 19980925 |
| | SE 1998-3710 | 19981029 |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |
| LEGAL REPRESENTATIVE: | Benton S. Duffett, Jr., BURNS, DOANE, SWECKER & MATHIS, L.L.P., P.O. Box 1404, Alexandria, VA, 22313-1404 |
| NUMBER OF CLAIMS: | 29 |
| EXEMPLARY CLAIM: | 1 |
| LINE COUNT: | 1211 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to pharmaceutical compositions for the treatment of spinal disorders caused by the liberation of TNF-.alpha. comprising an effective amount of a TNF-.alpha. inhibitor, as well as a method for treatment of such disorders, and the use of TNF-.alpha. inhibitors in the preparation of pharmaceutical compositions for such treatment.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 11 OF 21 USPATFULL

| | |
|---|---|
| ACCESSION NUMBER: | 2001:165573 USPATFULL |
| TITLE: | Non-invasive method for detecting target RNA |
| INVENTOR(S): | Iversen, Patrick L., Corvallis, OR, United States |
| PATENT ASSIGNEE(S): | AVI BioPharma, Inc. (U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|

PATENT INFORMATION: US 2001024783 A1 20010927
APPLICATION INFO.: US 2000-736920 A1 20001213 (9)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-493494, filed on 28 Jan 2000, PENDING

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1999-117846P | 19990129 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: IOTA PI LAW GROUP, 350 CAMBRIDGE AVENUE SUITE 250, P O BOX 60850, PALO ALTO, CA, 94306-0850
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 2004
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of detecting in a subject, the occurrence of a base-specific intracellular binding event involving a single-stranded target RNA, is disclosed. The method includes administering to the subject an oligomeric antisense compound having (i) from 8 to 40 bases, including a targeting base sequence that is complementary to a portion of the target RNA, (ii) a Tm, with respect to binding to a complementary RNA sequence, of greater than about 50.degree. C., and (iii) an ability to be actively taken up by mammalian cells, and (iv) conferring resistance of complementary RNA hybridized with the agent to RnaseH. Where the compound is administered in uncomplexed form, it preferably has a substantially backbone. At a selected time after said administering the agent, a sample of a body fluid is obtained from the subject, and the presence in the sample of a nuclease-resistant heteroduplex composed of the antisense oligomer and the complementary portion of the target RNA is detected. The method is useful, for example, for detecting levels of gene expression, biochemical or physiological states that are characterized by expression of certain genes, genetic mutations, and the presence and identity of infective viral or bacterial agents. Also disclosed are arrays, kits and antibodies employed in carrying out the method.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 12 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:256810 BIOSIS
DOCUMENT NUMBER: PREV200100256810
TITLE: p62/ZIP plays a role in regulation of NGF-mediated NF-kappaB activation.
AUTHOR(S): Paulk, Jessica M. (1); Wooten, Marie W. (1)
CORPORATE SOURCE: (1) Auburn University, 331 Funchess Hall, Auburn, AL, 36849 USA
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1163. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Zeta Protein kinase C interacting protein, p62/ZIP, is part of the transcription factor nuclear factor-kappa B (NF-kappaB) for both IL-**1** and **TNF receptors**. NF-kappa B is activated by nerve growth factor (NGF) treatment of pheochromocytoma (PC12) cells. We hypothesized that p62 may serve to regulate NGFs properties. To test

this hypothesis, p62 was overexpressed or **antisense** p62 was used to deplete cells of p62 protein via transient transfection. After stimulating the transfected cells with NGF, survivability, differentiation and NF-kappa B activation were examined. Cells overexpressing p62 displayed enhanced survival compared to control cells in a serum free environment. By comparison transfection of **antisense** p62 decreased survival compared to control. Effects of p62 on NGF-induced neurite outgrowth were determined. p62 overexpression enhanced neurite outgrowth compared to control cells, whereas those cells transfected with **antisense** p62 displayed reduction in neurites. In addition, p65 ReIA translocation to the nucleus was examined by both immunostaining and a kappa B reporter assay. Transfection of increasing concentrations of p62 into PC12 cells enhanced NGF-induced NF-kappa B activity in a dose-dependent manner. By comparison, p62 blocked NGF induced NF-kappa B activity. Together, these results reveal that p62 plays a crucial role in both NF-kappa B activation coupled to survival and differentiation of PC12 cells.

L6 ANSWER 13 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

ACCESSION NUMBER: 2001:138582 BIOSIS
DOCUMENT NUMBER: PREV200100138582
TITLE: Genes regulated in human breast cancer cells overexpressing manganese-containing superoxide dismutase.
AUTHOR(S): Li, Zhongkui; Khaletskiy, Alexander; Wang, Jianyi; Wong, Jeffrey Y. C.; Oberley, Larry W.; Li, Jian-Jian (1)
CORPORATE SOURCE: (1) Department of Radiation Research, Beckman Research Institute, City of Hope National Medical Center, 1500 Duarte Road, H115 Halper South Building, Duarte, CA, 91010-3000: jjli@coh.org USA
SOURCE: Free Radical Biology & Medicine, (February 1, 2001) Vol. 30, No. 3, pp. 260-267. print.
ISSN: 0891-5849.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The mitochondrial antioxidant enzyme manganese-containing superoxide dismutase (MnSOD) functions as a tumor suppressor gene. Reconstitution of MnSOD expression in several human cancer cell lines leads to reversion of malignancy and induces a resistant phenotype to the cytotoxic effects of TNF and hyperthermia. The signaling pathways that underlie these phenotypic changes in MnSOD-overexpressing cells are unknown, although alterations in the activity of several redox-sensitive transcription factors, including AP-1 and NF-kappaB, have been observed. To determine the downstream signaling molecules involved in MnSOD-induced cell resistant phenotype, in the present study we analyzed the expression profile of several groups of genes related to stress response, DNA repair, and apoptosis, in a human breast cancer MCF-7 cell line overexpressing MnSOD (MCF+SOD). Of 588 genes examined, 5 (0.85%) were up-regulated (2-42-fold), and 11 (1.9%) were down-regulated (2-33-fold) in the MCF+SOD cells compared to the parental MCF-7 cells. The five up-regulated genes were MET, GADD153, CD9, alpha-catenin and plakoglobin. The genes with the most significant down-regulation included: vascular endothelial growth factor **receptor 1**, **TNF**-alpha converting enzyme, and interleukin-1beta. GADD153 (involved in the repair of DNA double strand breaks) showed a 33-fold increase in microarray analysis and these results were confirmed by RT-PCR. To further determine the specificity in MnSOD-induced gene regulation, MCF+SOD cells were stably transfected with an **antisense** MnSOD sequence whose expression was controlled by a tetracycline-inducible regulator. Expression of three up-regulated genes was measured after induction of **antisense** MnSOD expression. Interestingly, expression level of GADD153 but not MET

or CD9 was reduced 24 h after **antisense** MnSOD induction. Together, these results suggest that reconstitution of MnSOD in tumor cells can specifically modulate the expression of down-stream effector genes. GADD153 and other elements observed in the MCF+SOD cells may play a key role in signaling the MnSOD-induced cell phenotypic change.

L6 ANSWER 14 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4

ACCESSION NUMBER: 2000:468362 BIOSIS
DOCUMENT NUMBER: PREV200000468362
TITLE: Mechanism of chronic obstructive uropathy: Increased expression of apoptosis-promoting molecules.
AUTHOR(S): Choi, Yeong-Jin; Baranowska-Daca, Elzbieta; Nguyen, Vinh; Koji, Takehiko; Ballantyne, Christie M.; Sheikh-Hamad, David; Suki, Wadi N.; Truong, Luan D. (1)
CORPORATE SOURCE: (1) Department of Pathology, Methodist Hospital, 6565 Fannin, Houston, TX, 77030 USA
SOURCE: Kidney International, (October, 2000) Vol. 58, No. 4, pp. 1481-1491. print.
ISSN: 0085-2538.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: We have demonstrated that renal tubular and interstitial cells undergo pronounced apoptosis during the course of chronic obstructive uropathy (COU). Apoptosis is a complex cellular process consisting of multiple steps, each of which is mediated by families of related molecules. These families may include receptor/ligand molecules such as Fas, Fas ligand, **tumor necrosis factor receptor-1** (TNFR-1), and TNF-related apoptosis inducing ligand (TRAIL); signal transduction adapter molecules such as Fas-associated death domain (FADD), TNFR-1 associated death domain (TRADD), receptor-interacting protein (RIP), Fas-associated factor (FAF), and Fas-associated phosphatase (FAP); or effector molecules such as caspases. However, the mechanism of tubular cell apoptosis, as well as the pathogenetic relevance of these apoptosis-related molecules in COU, remains poorly understood. Methods: Kidneys were harvested from sham-operated control mice and mice with COU created by left ureter ligation sacrificed in groups of three at days 4, 15, 30, and 45. To detect apoptotic tubular and interstitial cells, in situ end labeling of fragmented DNA was performed. To detect the expression of apoptosis-related molecules, ribonuclease protection assay was used with specific **antisense** RNA probes for Fas, Fas ligand, TNFR-1, TRAIL, FADD, TRADD, RIP, FAF, FAP, and caspase-8. Immunostaining for Fas, Fas ligand, TRAIL, TRADD, RIP, and caspase-8 was also performed. To assess the role of these molecules in COU-associated renal cell apoptosis, the frequencies of apoptotic tubular and interstitial cells were separately quantitated for each experimental time point, and their patterns of variation were correlated with those of apoptosis-related molecules. Results: The obstructed kidneys displayed increased apoptosis of both tubular and interstitial cells. Tubular cell apoptosis appeared at day 4 after ureter ligation, peaked (fivefold of control) at day 15, and decreased gradually until the end of the experiment. In contrast, interstitial cell apoptosis sustained a progressive increase throughout the experiment. Apoptosis was minimal at all experimental time points for control and contralateral kidneys. Compared with control and contralateral kidneys, the ligated kidneys displayed a dynamic expression of mRNAs for many apoptosis-related molecules, which included an up to threefold increase for Fas, Fas ligand, TNF-R1, TRAIL, TRADD, RIP, and caspase-8, and an up to twofold increase for FADD and FAP, but there was little change for FAF. These mRNAs increased between days 4 and 15, decreased until day 30, but then increased again until day 45. The rise and fall of

mRNAs between days 4 and 30 paralleled a similar fluctuation in tubular cell apoptosis in that period. The subsequent increase of mRNAs was correlated with a continuous rise of interstitial cell apoptosis. We demonstrated a positive immunostaining for Fas and Fas ligand in the tubular cells at early time points as well as in interstitial inflammatory cells at later time points. Although increased expression of TRAIL, TRADD, RIP, and caspase-8 was noted in tubular cells, there was no staining for these molecules in interstitial cells. Conclusion: The current study documents a dynamic expression of several molecules that are known to mediate the most crucial steps of apoptosis. It implicates these molecules in COU-associated renal cell apoptosis and in the pathogenesis of this condition. It also lays the foundation for interventional studies, including genetic engineering, to evaluate the molecular control of apoptosis associated with COU.

L6 ANSWER 15 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
ACCESSION NUMBER: 2000:277936 BIOSIS
DOCUMENT NUMBER: PREV200000277936
TITLE: **Antisense** inhibition of **TNFR1** expression.
AUTHOR(S): Baker, Brenda F. (1); Cowsert, Lex M.
CORPORATE SOURCE: (1) Carlsbad, CA USA
ASSIGNEE: Isis Pharmaceuticals Inc.
PATENT INFORMATION: US 6007995 December 28, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 28, 1999) Vol. 1229, No. 4, pp. No pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of **TNFR1**. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding **TNFR1**. Methods of using these compounds for modulation of **TNFR1** expression and for treatment of diseases associated with expression of **TNFR1** are provided.

L6 ANSWER 16 OF 21 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:306599 CA
TITLE: Antisense oligonucleotides capable of binding to multiple targets and their use in the treatment of respiratory disease
INVENTOR(S): Nyce, Jonathan W.
PATENT ASSIGNEE(S): East Carolina University, USA
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9913886 | A1 | 19990325 | WO 1998-US19419 | 19980917 |

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| CA 2304312 | AA | 19990325 | CA 1998-2304312 | 19980917 |
| AU 9893951 | A1 | 19990405 | AU 1998-93951 | 19980917 |
| EP 1019065 | A1 | 20000719 | EP 1998-947089 | 19980917 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI | | | | |
| BR 9812650 | A | 20000822 | BR 1998-12650 | 19980917 |

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|---|---|---|---|
| PRIORITY APPLN. INFO.: | US 1997-59160P | P | 19970917 |
| | US 1998-93972 | A | 19980609 |
| | WO 1998-US19419 | W | 19980917 |

AB Antisense oligonucleotides carrying sequences that will allow them to bind to more than one mRNA in a target cell are described. Such oligonucleotides can be used as a single treatment for diseases having more than one contributing pathway. In particular, oligonucleotides effective against genes involved in the etiol. of respiratory disease are targeted. Preferably, the oligonucleotides are low in adenosine (.ltoreq.15%) and may have adenosines substituted with analogs. These oligonucleotides are targeted to high (G+C) sequences within mRNAs. Thus, phosphorothioate antisense oligonucleotide (HAdA1AS, 5'-gatggagggcggcatggcggg-3') designed for the adenosine A1 receptor is provided. HAdA1AS significantly and specifically reduces the in vivo response to adenosine challenge in a dose-dependent manner, is effective in protection against aeroallergen-induced bronchoconstriction (house dust mite), has an unexpected long-term duration of effect (8.3 days for both PC50 adenosine and resistance), and is free of side effects that might be toxic to the recipient. Such oligonucleotides may be used for treating a disease or condition assocd. with lung airway, such as bronchoconstriction, inflammation, or allergies.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 21 USPATFULL

| | |
|---|---|
| ACCESSION NUMBER: | 1998:48258 USPATFULL |
| TITLE: | Targeted gene expression using preproendothelin-1 promoters |
| INVENTOR(S): | Harats, Dror, Ramat-Gan, Israel<br>Kurihara, Hiroki, Toyko, Japan<br>Belloni, Paula Nanette, Moss Beach, CA, United States<br>Sigal, Charles Elliott, San Francisco, CA, United States |
| PATENT ASSIGNEE(S): | Syntex (U.S.A.) Inc., Palo Alto, CA, United States (U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 5747340 | | 19980505 |
| APPLICATION INFO.: | US 1995-395742 | | 19950228 (8) |
| RELATED APPLN. INFO.: | Continuation-in-part of Ser. No. US 1994-254015, filed on 3 Jun 1994, now abandoned | | |
| DOCUMENT TYPE: | Utility | | |
| FILE SEGMENT: | Granted | | |
| PRIMARY EXAMINER: | Campbell, Bruce R. | | |
| LEGAL REPRESENTATIVE: | Heller Ehrman White & McAuliffe | | |
| NUMBER OF CLAIMS: | 15 | | |
| EXEMPLARY CLAIM: | 1 | | |
| NUMBER OF DRAWINGS: | 8 Drawing Figure(s); 8 Drawing Page(s) | | |
| LINE COUNT: | 851 | | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a vector for expression of a nucleic acid cassette in bronchial epithelial and vascular endothelial cells comprising a segment of the 5'-flanking region of the preproendothelin-1 gene, upstream from the transcription start site, the first exon of the

preproendothelin-1 gene, and a nucleic acid cassette, wherein the nucleic acid cassette is located within the first exon, in sequential and positional relationship for expression of the nucleic acid cassette.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 18 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6

ACCESSION NUMBER: 1998:227590 BIOSIS
DOCUMENT NUMBER: PREV199800227590
TITLE: Tumor necrosis factor-alpha confers resistance to hypoxic injury in the adult mammalian cardiac myocyte.
AUTHOR(S): Nakano, Masayuki; Knowlton, Anne A.; Dibbs, Ziad; Mann, Douglas L. (1)
CORPORATE SOURCE: (1) Cardiol. Section, VA Med. Cent., 2002 Holcombe Blvd., Houston, TX 77030 USA
SOURCE: Circulation, (April 14, 1998) Vol. 97, No. 14, pp. 1392-1400.
ISSN: 0009-7322.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Background-Previous studies in isolated cardiac myocytes have shown that tumor necrosis factor (TNF)-alpha provokes increased expression of 27- and 70-kD stress proteins as well as manganese superoxide dismutase, suggesting that TNF-alpha might play a role in mediating stress responses in the heart. Methods and Results-To determine whether TNF-alpha stimulation would protect isolated cardiac myocytes against environmental stress, myocyte cultures were pretreated with TNF-alpha for 12 hours and then subjected to continuous hypoxic injury (O2 content, 3 to 5 ppm) for 12 hours, followed by reoxygenation. Cell injury was assessed in terms of lactic dehydrogenase (LDH) release, 45Ca2+ uptake, and MTT metabolism. Pretreatment with TNF-alpha concentrations gtoreq 50 U/mL significantly attenuated LDH release by hypoxic cells compared with diluent-treated hypoxic cells. Similar findings were observed with respect to 45Ca2+ Uptake and MTT metabolism in TNF-alpha-pretreated cells that were subjected to prolonged hypoxia. To determine the mechanism for the TNF-alpha-induced protective effect, the cells were pretreated with heat shock protein (HSP) 72 **antisense** oligonucleotides. These studies showed that the protective effect of TNF-alpha was not inhibited by **antisense** oligonucleotides, despite use of a concentration of **antisense** that was sufficient to attenuate the TNF-alpha-induced increase in HSP 72 expression. Subsequent studies using mutated TNF ligands showed that activation of both types **1** and 2 **TNF receptors** was sufficient to confer a protective response in isolated cardiac exclusive of the protective response conferred by HSP 72 expression.

L6 ANSWER 19 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7

ACCESSION NUMBER: 1998:482723 BIOSIS
DOCUMENT NUMBER: PREV199800482723
TITLE: Autocrine self-elimination of cultured ovarian cancer cells by tumour necrosis factor alpha (TNF-alpha.
AUTHOR(S): Simonitsch, I.; Krupitza, G. (1)
CORPORATE SOURCE: (1) Inst. Clinical Pathol., Univ. Vienna, Waehringer Guertel 18-20, 1090 Vienna Austria
SOURCE: British Journal of Cancer, (Oct., 1998) Vol. 78, No. 7, pp. 862-870.
ISSN: 0007-0920.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Human ovarian adenocarcinoma cells N.1 secrete an autocrine activity that

stimulates active cell death under serum-reduced conditions. To substitute the autocrine activity by a single physiological component, 28 cytokines, growth factors and biomodulators were tested (interleukin 1alpha (IL-1alpha), IL-1beta, IL-2, IL-3, IL-4, IL-6, IL-10, IL-11, stem cell factor (SCF), platelet-derived growth factor (PDGF), acid fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF-1), IGF-2, insulin, macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), oncostatin, RANTES (regulated on activation normal T cell expressed and secreted), angiogenin, leukaemia inhibitory factor (LIF), erythropoietin (EPO), interferon alpha (INF-alpha), INF-gamma, transferrin, tumour necrosis factor alpha (TNF-alpha), TNF-beta and bovine serum albumin for control reasons). In these experiments, only TNF-alpha and TNF-beta rapidly induced apoptosis. TNF-alpha and **TNF-receptor 1** were expressed by N.1 cells, and the secretion of TNF-alpha was verified by enzyme-linked immunosorbent assay (ELISA). Autocrine factor-triggered apoptosis was inhibited when conditioned supernatant was preincubated with anti-TNF-alpha antibody. These findings suggested that the apoptosis-inducing component of the N.1 autocrine activity was TNF-alpha. In the presence of **antisense** c-myc oligonucleotides, induction of cell death by autocrine factor was partly inhibited. Autocrine factor and TNF-alpha stimulated transcription of the invasiveness-related protease plasminogen activator/urokinase mRNA (upa) with similar kinetics. When N.1 cells were exposed to purified plasminogen activator/urokinase protein (uPA), cell matrix contact was disrupted. Thus, uPA might serve a physiological role during TNF-induced apoptosis by affecting the interactions between cells and the basal membrane, thereby facilitating anoikis. This mechanistic study, which was restricted to a single human ovarian carcinoma model cell line (N.1), provides evidence that N. 1 maintains the capacity to undergo c-myc-dependent apoptosis by the TNF-TNF-receptor pathway, and no additional pharmacological stimuli for induction of apoptosis are required.

L6 ANSWER 20 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8

ACCESSION NUMBER: 1997:126916 BIOSIS
DOCUMENT NUMBER: PREV199799418729
TITLE: Inhibition of p75 tumor necrosis factor receptor by antisense oligonucleotides increases hypoxic injury and beta-amyloid toxicity in human neuronal cell line.
AUTHOR(S): Shen, Yong (1); Li, Rena; Shiosaki, Kazumi
CORPORATE SOURCE: (1) Dep. Neurosci., 47C/AP10, Abbott Lab., Abbott Park, IL 60064 USA
SOURCE: Journal of Biological Chemistry, (1997) Vol. 272, No. 6, pp. 3550-3553.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Recent evidence indicates that tumor necrosis factor-alpha (TNF-alpha) is up-regulated following brain injury and in neurodegenerative disorders such as stroke, multiple sclerosis, Parkinson's disease, and Alzheimer's disease. TNF-alpha elicits its biological effects through two distinct TNF receptor (TNFR) subtypes: p55 TNFR (**TNFR1**) and p75 TNFR (TNFR2). Studies have demonstrated that the p55 TNFR contributes to cell death, whereas the role of the p75 TNFR in neuronal viability is unclear. To better understand the role of p75 TNFR, we treated human neuronal SH-SY5Y cells with phosphorothioate-modified **antisense** oligonucleotides (ASO) for p75 TNFR and established that ASO inhibited p75 TNFR expression. Treatment of SH-SY5Y cells with ASO alone did not affect cell viability, whereas treatment with both ASO and human TNF-alpha significantly increased cell death relative to treatment with TNF-alpha alone. Moreover,

addition of ASO significantly increased the level of cell injury observed following hypoxic conditions or exposure of beta-amyloid peptide. These results indicate that inhibition of p75 TNFR using ASO increases the vulnerability of neurotypic cells to insults and suggest that the p75 TNFR may not be required for normal neuronal cell viability but rather plays a protective role following injury.

L6 ANSWER 21 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9

ACCESSION NUMBER: 1993:585254 BIOSIS
DOCUMENT NUMBER: PREV199497004624
TITLE: Overexpression of major heat shock protein hsp70 inhibits tumor necrosis factor-induced activation of phospholipase A-2.
AUTHOR(S): Jaattela, Marja
CORPORATE SOURCE: Dep. Tum. Cell Biol., Danish Cancer Society Res. Cent., Div. Cancer Biol., DK-2100 Copenhagen Denmark
SOURCE: Journal of Immunology, (1993) Vol. 151, No. 8, pp. 4286-4294.
ISSN: 0022-1767.
DOCUMENT TYPE: Article
LANGUAGE: English

AB We have recently shown that major heat shock protein (hsp70) protects WEHI-S tumor cells from the cytotoxicity mediated by TNF. In the present study, the mechanism of hsp70-associated TNF resistance was investigated. Overexpression of human hsp70 or inhibition of endogenous hsp70 synthesis by expression of **antisense** hsp70 RNA did not change the ability of WEHI-S tumor cells to bind TNF or internalize and degrade the receptor-bound TNF. Moreover, TNF-induced activation of NF-kappa-B-like transcription factors was unaffected by altered levels of hsp70 as tested by electrophoretic mobility shift assay. Thus, it is unlikely that the resistance is due to changes in TNF receptors or in their ability to transduce signals leading to the regulation of genes, whose expression is regulated by NF-kappa-B-like transcription factors. The idea that hsp70-associated TNF resistance is independent of regulation of TNF-induced gene expression was further supported by the results showing that hsp70 protected WEHI-S cells from TNF-mediated killing also in the presence of inhibitors of either translation or transcription. Interestingly, TNF-induced activation of arachidonic acid metabolism correlated directly with their sensitivity to TNF and inversely with the amount of hsp70 in the cells. Furthermore, TNF-induced activation of arachidonic acid metabolism was inhibited in WEHI-S cells and two TNF-sensitive human cell lines by induction of the synthesis of endogenous heat shock proteins by heat shock. Even stronger inhibition of arachidonic acid metabolism was seen in WEHI cells rendered TNF-resistant by culturing them in the presence of increasing concentrations of TNF. These cells also had reduced numbers of type **1 TNF receptors**.
Overexpression of a low molecular weight heat shock protein hsp27 in WEHI-S cells had no effect on any of the parameters studied. These results show that both hsp70-mediated and TNF-induced TNF resistance are associated with a reduced activation of phospholipase A2 suggesting that phospholipase A-2 plays an essential role in TNF-mediated cytotoxicity and that hsp70 interferes with the signal transduction pathway leading to its activation.

=> s baker, B?/au; s cowsert, L?/au
L8 5377 BAKER, B?/AU

L9 489 COWSERT, L?/AU

=> s (l8 or l9) and l3
L10 10 (L8 OR L9) AND L3

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11 7 DUP REM L10 (3 DUPLICATES REMOVED)

=> s l11 and antisense
L12 7 L11 AND ANTISENSE

=> d l12 1-7 ibib abs

L12 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:277936 BIOSIS
DOCUMENT NUMBER: PREV200000277936
TITLE: **Antisense** inhibition of **TNFR1** expression.
AUTHOR(S): **Baker, Brenda F. (1); Cowsert, Lex M.**
CORPORATE SOURCE: (1) Carlsbad, CA USA
ASSIGNEE: Isis Pharmaceuticals Inc.
PATENT INFORMATION: US 6007995 December 28, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 28, 1999) Vol. 1229, No. 4, pp. No pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of **TNFR1**. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding **TNFR1**. Methods of using these compounds for modulation of **TNFR1** expression and for treatment of diseases associated with expression of **TNFR1** are provided.

L12 ANSWER 2 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 137:57583 CA
TITLE: Antisense modulation of tumor necrosis factor receptor-1 (TNFR1) expression for treatment of diseases
INVENTOR(S): Baker, Brenda F.; Cowsert, Lex M.; Zhang, Hong; Dean, Nicholas M.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002048168 | A1 | 20020620 | WO 2001-US51224 | 20011022 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-695451 A 20001024

AB Antisense compds., compns. and methods are provided for modulating the expression of TNFR1. The compns. comprise antisense compds., particularly antisense oligonucleotides, targeted to nucleic acids encoding TNFR1. Methods of using these compds. for modulation of TNFR1 expression and for treatment of diseases assocd. with expression of TNFR1 are provided. Diseases treated were liver injury, hepatitis and liver cancer.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 7 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 131:346559 CA

TITLE: **Antisense** modulation of sentrin expression

INVENTOR(S): **Baker, Brenda F.; Cowsert, Lex M.**

PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA

SOURCE: U.S., 29 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5985664 | A | 19991116 | US 1998-213768 | 19981217 |
| WO 2000036148 | A1 | 20000622 | WO 1999-US13205 | 19990610 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9946795 | A1 | 20000703 | AU 1999-46795 | 19990610 |

PRIORITY APPLN. INFO.: US 1998-213768 A 19981217
WO 1999-US13205 W 19990610

AB **Antisense** compds., compns. and methods are provided for modulating the expression of Sentrin. Sentrin (also known as UBL1, PIC1, SMP1, or SUMO-1) is a ubiquitin-like mol. which attaches to a protein but, unlike ubiquitin, conjugation results in protein trafficking and localization and not in labeling of target proteins for degrdn.; sentrin appears to binding to the death domain of the **TNFR1** receptor and play a role in apoptosis, as well as be involved in nuclear protein import. The compns. comprise **antisense** compds., particularly **antisense** oligonucleotides, targeted to nucleic acids encoding Sentrin. Phosphorothioated **antisense** oligonucleotides, as well as gapmers contg. 2'-methoxyethyl ribose modifications, yielded .gtoreq.25% inhibition of Sentrin expression. Methods of using these compds. for modulation of Sentrin expression and for treatment of diseases assocd. with expression of Sentrin are provided.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 7 USPATFULL

ACCESSION NUMBER: 2002:188252 USPATFULL

TITLE: **Antisense** modulation of RIP2 expression

INVENTOR(S): Ward, Donna T., Murrieta, CA, United States
**Cowsert, Lex M.**, Carlsbad, CA, United States

PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., Carlsbad, CA, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 6426221 | B1 | 20020730 | |
| APPLICATION INFO.: | US 2001-920663 | | 20010801 | (9) |

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: LeGuyader, John L.
ASSISTANT EXAMINER: Schmidt, M
LEGAL REPRESENTATIVE: Licata & Tyrrell P.C.
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 3059
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Antisense** compounds, compositions and methods are provided for modulating the expression of RIP2. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding RIP2. Methods of using these compounds for modulation of RIP2 expression and for treatment of diseases associated with expression of RIP2 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 5 OF 7 USPATFULL
ACCESSION NUMBER: 2002:129717 USPATFULL
TITLE: **Antisense** modulation of expression of tumor necrosis factor receptor-associated factors (TRAFs)
INVENTOR(S): **Baker, Brenda F.**, Carlsbad, CA, United States
**Cowsert, Lex M.**, Carlsbad, CA, United States
Monia, Brett P., La Costa, CA, United States
Xu, Xaoxing S., Maddison, NJ, United States
PATENT ASSIGNEE(S): ISIS Pharmaceuticals, Inc., Carlsbad, CA, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 6399297 | B1 | 20020604 | |
| APPLICATION INFO.: | US 1998-167109 | | 19981006 | (9) |

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Wang, Andrew
LEGAL REPRESENTATIVE: Licata & Tyrrell P.C.
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 2151
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods are provided for modulating the expression of tumor necrosis factor receptor-associated factor (TRAF). **Antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding TRAF are preferred. Methods of using these compounds for modulation of TRAF expression and for treatment of diseases associated with expression of TRAF are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 6 OF 7 USPATFULL
ACCESSION NUMBER: 2001:4534 USPATFULL
TITLE: **Antisense** inhibition of rank expression
INVENTOR(S): **Baker, Brenda F.**, Carlsbad, CA, United States

**Cowsert, Lex M.**, Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., Carlsbad, CA, United States (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6171860 | B1 | 20010109 |
| APPLICATION INFO.: | US 1999-435296 | | 19991105 (9) |

DOCUMENT TYPE: Patent
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: Zara, Jane
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 2574
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Antisense** compounds, compositions and methods are provided for inhibiting the expression of RANK. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding RANK. Methods of using these compounds for inhibition of RANK expression and for treatment of diseases associated with expression of RANK are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 7 OF 7 USPATFULL
ACCESSION NUMBER: 1999:117343 USPATFULL
TITLE: **Antisense** inhibition of cellular inhibitor of apoptosis-1 expression
INVENTOR(S): Bennett, C. Frank, Carlsbad, CA, United States
Ackermann, Elizabeth J., Solana Beach, CA, United States
**Cowsert, Lex M.**, Carlsbad, CA, United States
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 5958772 | | 19990928 |
| APPLICATION INFO.: | US 1998-205204 | | 19981203 (9) |

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: LeGuyader, John L.
LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 2755
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Antisense** compounds, compositions and methods are provided for modulating the expression of Cellular Inhibitor of Apoptosis-1. The compositions comprise **antisense** compounds, particularly **antisense** oligonucleotides, targeted to nucleic acids encoding Cellular Inhibitor of Apoptosis-1. Methods of using these compounds for modulation of Cellular Inhibitor of Apoptosis-1 expression and for treatment of diseases associated with expression of Cellular Inhibitor of Apoptosis-1 are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 104.36 | 104.57 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -2.95 | -2.95 |

STN INTERNATIONAL LOGOFF AT 16:33:36 ON 19 SEP 2002